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Differential effects of low frequency, low intensity (< 6 mG) nocturnal magnetic fields upon infiltration of mononuclear cells and numbers of mast cells in lewis rat brains

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Abstract

Immediately after inoculation to induce experimental allergic encephalomyelitis, 64 female Lewis rats were exposed to either a reference condition (< 10 nT) or to one of two frequencies (7 Hz, 40 Hz) of magnetic fields whose two intensities (either 50 nT or 500 nT) were amplitude-modulated for 6 min once per hour between midnight and 8 h for 15 nights. Rats that had been exposed to the 7 Hz, low intensity fields displayed fewer numbers of foci of infiltrations of mononuclear cells compared to all other groups that did not differ significantly from each other. Rats exposed to the 5 mG (500 nT), 40 Hz magnetic fields displayed more foci in the right thalamus while those exposed to the 5 mG, 7 Hz fields displayed more foci in the left thalamus. Numbers of mast cells within the thalamus were also affected by the treatments. These results suggest that weak magnetic fields can affect the infiltration of immunologically responsive cells and the presence of mast cells in brain parenchyma. Implications for the potential etiology of 'electromagnetic sensitivity' symptoms are discussed. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Immunosuppression; Vasculature; ELF magnetic field; Experimental allergic encephalomyelitis; Mast cells; Brain

1. Introduction

Experimental allergic encephalomyelitis (EAE), the animal model of Multiple Sclerosis, has been extensively studied to discern the mechanisms by which inflammation and demyelination occur within the central nervous system (Simmons et al., 1984). EAE is associated with overt (clinical) signs that include tail atonia, hindlimb paresis and, in the most extreme cases, complete paralysis. Infiltrations of mononuclear cells, specifically lymphocytes, into the brain occur as collections or foci of cells that are found around blood vessels. The density gradient of these cells suggest they originate from the vasculature (Pekarski et al., 1998).

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The occurrence of foci of lymphocytes within the parenchyma of brains of rats in which EAE was induced has been associated (Paul and Bolton, 1995) with compromise in the integrity of the blood brain barrier. Cook and Persinger (1999) found that even subclinical dosages of a combination of drugs (lithium and pilocarpine) that evoke status epilepticus at much larger dosages were associated with infiltrations of foci of lymphocytes within very specific structures such as the fornix. These data indicated that quantification of the numbers of foci within the brain parenchyma may be employed as sensitive indices of changes in the blood-brain-barrier associated with exposure to environmental stimuli whose effects might otherwise escape detection.

Recently we (Persinger et al., 1999) found that Lewis rats (following inoculation to induce EAE) exposed to 7 Hz, 50–60 nT amplitude-modulated magnetic fields for 6 min every hour for 8 h during the late scotophase showed a marked reduction in the severity of the overt signs of EAE compared to sham-field controls. The purpose of the following study was to discern if the numbers of foci within the brain were affected by exposure to either one of two frequencies of amplitude-modulated magnetic fields (7 Hz, 40 Hz) whose peak intensities were within the range of either 50 or 500 nT. An additional measure, the numbers of mast cells within (primarily) the diencephalon, was also included. These histologically conspicuous cells are sensitive to changes in environmental stimuli (Persinger, 1977, 1980, 1981).

2. Materials and methods

Sixty-four female Lewis rats (age 120–130 days), obtained from Charles River, Inc. (Montreal, Quebec), were employed as subjects. After the protocol had been approved by the Animal Care Committee, each rat received a 0.1 cc injection of 40 mg/kg of female Lewis rat spinal cord emulsified in Freund's complete adjuvant into the pad of each hindfoot (0.2 cc in total). Immediately following inoculation, the rats were weighed and placed two per cage.

The exposure apparatus consisted of two plastic cages (32 cm by 36 cm by 45 cm) each of which was wrapped around its major axis by wire (AWG 20). Each coil (30 Ω) was connected in parallel to a custom built device that controlled the amplitude modulation of the output from a Model EU 81A Heath–Schlumberger function generator. Two other identical cages, which housed the reference groups, were maintained 30 cm directly below the two coils.

The major axes of each coil and each of the four cages were in a N–S direction. The static background intensities (resultant values) within the exposure areas (no experimental fields activated but equipment connected and functioning) ranged between 30 000 and 38 000 nT according to a FM300 Vector Magnetometer (MacIntyre Electronics, Herndon, Virginia). Lighting within the four cages was supplied by overhead fluorescent lamps and was between 700 and 800 lux according to a Gossen Panlux meter. The temperature within the room which housed the apparatus and rats was maintained by thermostat between 20 and 21°C. The light:dark cycle was 12:12; night time was between 20 h and 8 h local time.

The Commodore computer was programmed to generate an amplitude-modulated field of either 7 Hz square waves or 40 Hz square waves for 5 min and 50 s, 8 times per night, beginning each hour from midnight through 0706 h local time. The temporal structure of the amplitude variations of the field was designed to accommodate the time constants involved in the temporal sensing of electromagnetic fields by cells as reported by Litovitz et al. (1997). Employing 10 μT magnetic fields (about 20 times stronger than our highest intensities), they found interpulse times of less than 100 ms and presentation of the frequency for at least 10 s were required to maintain the enhancement of ornithine decarboxylase activity.

In our study (see Fig. 1) there were 14 shifts, 14 s each, in the amplitudes (7 maxima, 7 minima with values 1/2 the maxima) of either the 7 or 40 Hz ripple frequency during the first 3 min and 20 s of the field presentation, a 48 s period of the minima, and then 14 shifts in the amplitude (7 peaks, 7 troughs), 7 s each during the last one min

and 42 s of the presentation. Each shift required 2 μs. During the 40 Hz amplitude modulations the two 'time constants' analogous to those reported by Litovitz et al. (1997) were 25 ms and between 7 s and 14 s. These values would meet their empirical criteria. In addition the pattern of the amplitude modulation was designed to accommodate the natural shapes of sudden storm commencements. These sudden shifts in the intensity of the geomagnetic field have median durations of about 6 min and amplitudes that range from a few nT to about 100 nT (Mayaud, 1975).

In each of eight separate blocks of experiments eight rats were exposed to the experimental situation. During the 500 nT condition, eight rats were exposed to the 40 Hz amplitude modulated fields while another eight rats were exposed to the 7 Hz amplitude modulated fields. During the 50 nT condition, eight rats were exposed to the 40 Hz amplitude modulated fields and another eight rats were exposed to the 7 Hz amplitude modulated fields. During the four experiments when the intensities within the coils were 500 nT, extended fields of between 30 and 40 nT were generated into the control cages (16 rats). These rats served as comparisons to discern if any effects were specific to spurious factors associated with living within the coil or due to the intensities of the experimental magnetic fields. Another 16 rats, that were maintained within the reference cages below the coils when 50 nT fields were generated within the coils, were not exposed to any discernable extended fields (< 10 nT) and served as the control group.

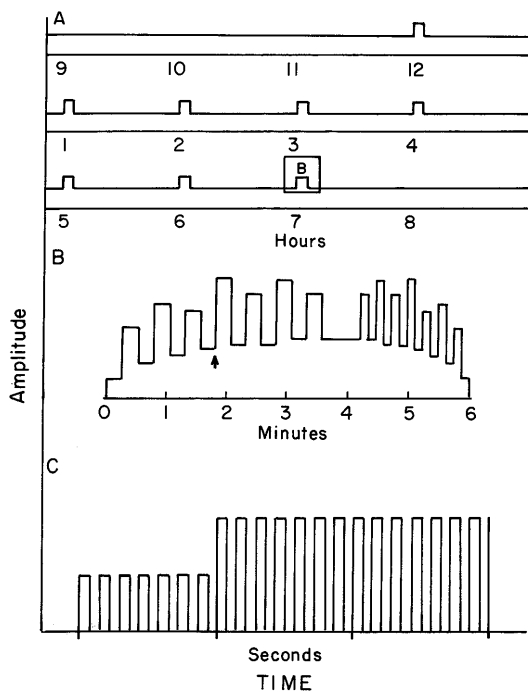

Fig. 1. Temporal characteristics of the presentation of the experimental magnetic field once per hour (A). The amplitude profile for either the 40 or 7 Hz square wave magnetic fields during this hourly presentation whose peak was either 50 or 500 nT, for the 6 min of presentation is shown in (B). (C) shows a brief increment of the shift in amplitude for the 7 Hz wave.

In all experiments, the times and presentations of the fields by the computer were recorded on its log. The presence and intensities of the fields were verified manually every second night by a Metex M-3800 digital multimeter and sensor (Electric Field Measurement, W. Stockbridge, MA 01266). The field strengths along the long axis of the cages within the coil decreased by 40% of the peak value along the outer edge while the field strengths within the cages receiving the extended fields exhibited a change of less than 10% across this distance.

After 15 days of exposure, brains were removed and immediately placed in an ethanol-formalin-acetic acid (EFA) solution for a minimum of 24 h. The brains were then processed, embedded in paraffin, and cut at 10 μm from the level of the superior olive of the midbrain to the genu of the corpus callosum. Every 10th section was saved and stained with toluidine blue-O (0.2 g/100 ml of 60% ethanol) to view the numbers of foci of mononuclear cells (Cook and Persinger, 1999) and mast cells (Persinger, 1980). This combination of fixation and stain clearly differentiates the infiltrating lymphocytes around blood vessels and the mast cells (which stain as deep purple with some metachromasia) from other cells. A mast cell was counted only if a portion of its nucleus was obvious. Total numbers of mast cells and numbers of foci for each of 17 equally spaced sections were measured at $400\times$. All nomenclature and identification of structures were refer-

Table 1
Experimental design for exposure and data analysis

Magnetic Field (nT)	Condition	7 Hz	40 Hz
Experimental design for exposure			
<10	Stray field from 50 nT	$n=8$	$n=8$
30–40	Stray field from 500 nT	$n=8$	$n=8$
50	'Low' experimental field	$n=8$	$n=8$
500	'High' experimental field	$n=8$	$n=8$
Experimental plan for data analyses			
<10	Control group	$n=8$	$n=8$
30–50	Low intensity MF group	$n=16$	$n=16$
500	High intensity MF group	$n=8$	$n=8$

enced to Paxinos and Watson (1986). The histologist (first author) was not familiar with the experimental condition of the brain during the cytometry. Inter-rater reliability for counts of mast cells or foci was greater than $r=0.95$.

Because there were no statistically significant differences for the numbers of mast cells or number of infiltrations of lymphocytes between the rats exposed either directly to the 50 nT fields (7 or 40 Hz) within the coils or indirectly in the cages (average peak field strengths between 30 and 40 nT) below the coils when they were activated at 500 nT, these pairs of groups were combined into the low intensity 7 Hz condition and the low intensity 40 Hz condition. The remaining groups were the control condition (less than 10 nT), the high intensity 7 Hz condition and the high intensity 40 Hz condition. The experimental designs for exposure and for data analyses are shown in Table 1.

Three way analysis of variance with one level repeated (left, middle, right side) and two within subject factors (intensity, frequency) were completed for the total numbers of foci within the whole brain and the following specific regions: the thalamus, hypothalamus, all tract systems, the subcortical telencephalon, the midbrain, and the myelencephalon. The fornix was analyzed separately because of its sensitivity to infiltration from subclinical injections of combinations of compounds, such as lithium and pilocarpine (Cook and Persinger, 1999) that evoke electrical seizures. Structures were defined as medial if the majority of their areas were within -1 to $+1$ mm of the midline, e.g. central grey, many of the commissures, the triangular septum. One way analysis of variance for the numbers of foci within these regions were completed to obtain the means and standard errors of the mean and to simplify visual presentation of the data.

Three way analyses of variance with one within subject (treatment) and two repeated (lateral axis: left-side, middle, right-side, and, caudal-rostral axis of the diencephalon: caudal 1/3, middle 1/3 and anterior 1/3) for the numbers of mast cells. For graphic presentation, the data were also analyzed as a function of the five groups: control, low intensity 7 Hz, high intensity 7 Hz, low intensity 40 Hz, and high intensity 40 Hz. One way analysis of variance was completed for the total numbers of mast cells within all sections as a function of the five treatments.

All analyses involved SPSS software on a VAX computer. Post hoc tests involved Tukey's set at $P<0.05$. Eta-squared values, which are quantitative indicators of the effect-size or the amount of variance in the numbers of foci or mast cells due to the treatments, were also calculated to allow perspective regarding the potential practical significance of the changes.

3. Results

The qualitative characteristics of the foci of concentrations of lymphocytes within the brain

parenchyma were similar to those reported previously (Cook and Persinger, 1999). Mast cells displayed their typical morphology (Persinger, 1977). The means and standard errors of the mean for the square root of the total numbers of foci measured for all coronal sections for each rat as a function of treatment are shown in Fig. 2 (upper panel). Square-root transformations were required to minimize the heterogeneity of variance between treatments. The two way analysis of variance showed a statistically significant effect for frequency [$F(1, 58) = 8.03$, $P < 0.01$, $\eta^2 = 0.13$] but not intensity [$F(2, 58) < 1.00$, $P > 0.05$].

However, the interaction between frequency and intensity [$F(2, 58) = 2.87$, $P < 0.05$] was also statistically significant. Post hoc analysis indicated that the primary source of the interaction as due to the fewer numbers of foci within the brains of the rats that had been exposed to the low intensity, 7 Hz amplitude modulated field compared to the brains of rats that had been exposed to the control and low intensity, 40 Hz amplitude modulated fields.

The means and standard errors of the mean for the numbers of foci within the fornix, which reflected the general pattern for all white matter (tracts) within the brain, are shown in the second

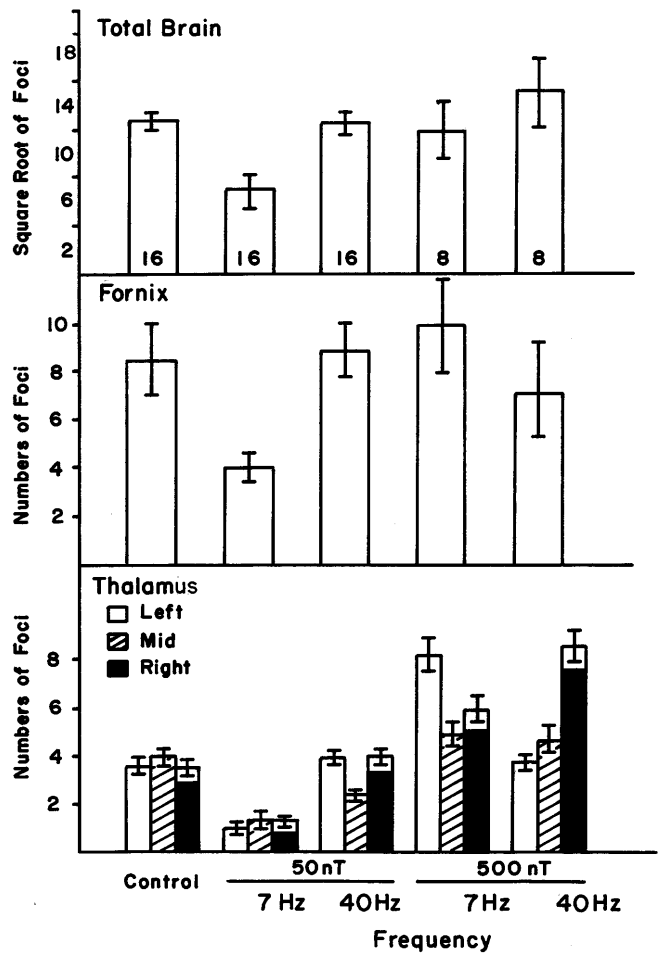

Fig. 2. Square root of the total numbers of foci of lymphocytes within all sections of the brains of rats exposed to various treatments (horizontal axis). Means for the total numbers of foci found within the fornix and within the left, middle, and right thalamus as a function of treatment are also shown. Vertical lines indicate standard errors of the mean.

panel of Fig. 2 for the five treatments. Two way analysis of variance again demonstrated a statistically significant interaction between intensity and frequency [$F(2, 58) = 5.30$, $P < 0.01$; $\eta^2 = 0.12$, i.e. 12% of the variance explained] as well as differences between the two frequencies [$F(2, 58) = 9.05$, $P < 0.01$]. Post hoc analysis indicated that the primary source of the interaction was due to the reduction of foci within the fornices of rats that had been exposed to the low intensity, 7 Hz fields compared to all other groups.

Perhaps the most revealing effect occurred within the thalamus. A three-way interaction occurred between intensity, frequency and the laterality (left, middle, and right) within the thalamus for the total numbers of foci of mononuclear cells [$F(4, 116) = 3.53$, $P < 0.01$; $\eta^2 = 11\%$]. Post hoc analysis indicated that the major source of this interaction (Fig. 2, middle panel) was due to the greater numbers of foci within the right thalamus for rats that had been exposed to 40 Hz, high intensity fields relative to the greater numbers of foci within the left thalamus for rats that had been exposed to the 7 Hz, high intensity fields. This asymmetry was not observed for the controls or the rats that had been exposed to the low intensity 7 Hz fields.

The only other statistically significant effect within the thalamus was due to the greater numbers of foci [$F(2, 58) = 3.93$, $P < 0.05$; $\eta^2 = 11\%$] within the brains of rats, in general, that had been exposed to the high intensity fields (regardless of frequency) compared to the low intensity and controls that did not differ from each other. Only statistically significant differences ($P < 0.01$) in numbers of foci between intensities (more foci associated with the high intensities compared to the low intensity and control groups) were noted within the midbrain, subcortical telencephalon and metencephalon. There were no significant main effects or interactions between intensity and frequency for the numbers of foci within the hypothalamus.

Approximately 40 Paxinos and Watson structures within the thalamus displayed mast cells. Four-way analysis of variance with two levels repeated (caudal-rostral 1/3 s; left side and right side) and two within subject factors (intensity, frequency) for the total numbers of mast cells (sum of numbers of cells within 10, non-adjacent 10 μm coronal sections) showed statistically significant differences between intensities [$F(2, 58) = 4.17$, $P < 0.05$; $\eta^2 = 12\%$] and frequency [$F(1, 58) = 14.91$, $P < 0.001$; $\eta^2 = 21\%$]. The means and standard errors of the mean for the control, frequency and intensity conditions are also shown in Fig. 3. The numbers of mast cells for the left and right sides of the thalamus are shown, even though there were no statistically significant differences, in order to illustrate the degree of consistency in measurements.

In addition to the significant differences between the numbers of mast cells within the anterior, middle, and posterior portions of the thalamus [$F(2, 116) = 266.56$, $P < 0.001$] there were statistically significant interactions between intensity of the fields (regardless of frequency) and the three levels of the thalamus [$F(4, 116) = 5.01$, partial $\eta^2 = 15\%$] and between the three levels along the neuroaxis, frequency, and intensity [$F(4, 116) = 4.48$, $P < 0.01$; partial $\eta^2 = 13\%$].

Post hoc analyses for the former interaction indicated that more mast cells were found within the middle thalamus (compared to the other two levels) of rats that had been exposed to the high intensity fields compared to the control and low intensity fields. Post hoc analysis for the latter interaction indicated that the major source was due to the greater numbers of mast cells in the posterior thalamus of rats that had been exposed to the low intensity 40 Hz fields compared to thalamus of rats exposed to the control and low intensity 7 Hz fields, but (1) the greater numbers of mast cells within the middle thalamus for rats that had been exposed to the high intensity 40 Hz fields compared to the thalamus of rats exposed to the control and low intensity 7 Hz fields; and (2) the greater number of mast cells within the anterior thalamus of the rats that had been exposed to the 40 Hz high intensity fields compared to the this area for rats that had been exposed to the low intensity 40 Hz fields.

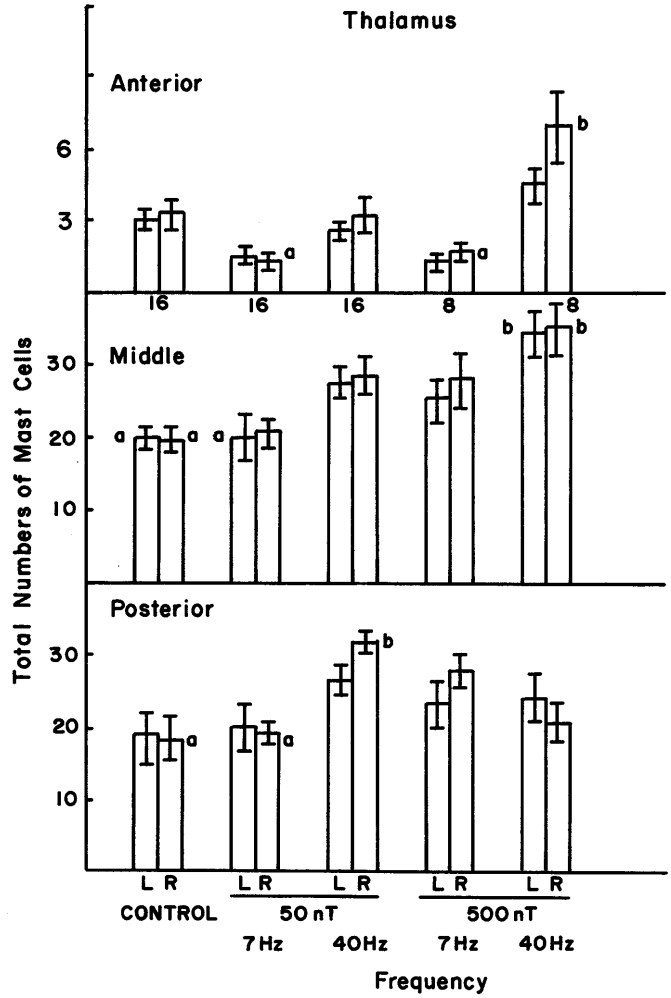

Fig. 3. Mean of the total numbers of mast cells found within the left and right sides of the anterior, middle, and posterior portions of the thalamus as a function of exposure to control or to high or low 7 or 40 Hz amplitude-modulated magnetic fields. Vertical lines indicate standard errors of the mean. A vs B = $P < 0.05$.

4. Discussion

The results of this study indicated that brains of rats inoculated to induce EAE responded differently to weak magnetic fields whose intensities are within the range measured within modern living environments. The rats exposed to the 7 Hz, 0.3 mG (30 nT) to 0.5 mG (50 nT) magnetic fields for 15 successive nights exhibited a reduction in the total numbers of foci of lymphocytes throughout brain space relative to all other treatments. Because the rats that had been exposed either to the direct 50 nT, 7 Hz fields within the coils or that had been exposed indirectly to this range of intensity from the stray fields generated during the 5 mG (500 nT) experiments did not differ significantly, the probability is high that the effects were specific to this range of intensities and frequency and were not an artifact of living within the coils.

One of the difficulties encountered by early toxicologists and pharmacologists who obtained their treatments from plants was that extractions from unspecified sources with unknown purities often produced ambiguous and even contradic-

tory results. Only when pharmacologists quantified the chemical structures of the active ingredients and understood their biochemical consequences within the cell did the reliability of treatment increase dramatically. Whereas the complex, spatial structures of chemicals may determine their effects upon the brain, the complex, temporal structures of magnetic fields may determine their specific effects upon its function. It is possible that the biological significance of the specificity of the temporal pattern of the applied magnetic field is greater than previously suspected. The effects of simple sinusoidal fields of a given frequency with a fixed magnitude compared to the effects of more complex fields might be analogous to administering a non-specific vs a highly specific chemical agent.

The observation of more foci within the right thalamus in rats that had been exposed to the 40 Hz, high intensity field but more foci within the left thalamus of rats that had been exposed to the 7 Hz high intensity field indicates that neural structures within the left side and right side of the thalamus (as well as their projections to ipsilateral areas within the cerebral cortices) may be responsive to different frequencies when their amplitudes are modulated. These results, in conjunction with the differential response of mast cells within the middle, posterior, and anterior thalamus to the treatments, support the possibility that different regions of the brain may not exhibit homogeneous responses to different frequencies and intensities of complex magnetic fields and may help explain the successful treatment of multiple sclerosis with magnetic fields (Sandyk, 1992). These results might be analogous to the more well known differential sensitivity within the brain to toxicological agents that varies as a function of the regional distributions of different subtypes of receptors.

The results of this study may have practical, epidemiological implications for toxicologists. For example background intensities for magnetic fields of 60 Hz fields, distal to electronic sources, are usually between 0.1 mG (10 nT) and 5 mG (500 nT). Our field measurements in houses, particularly those that were poorly grounded or contained irregular wiring, have shown periods of enhanced amplitudes of 60 Hz intensities between 2 and 15 mG within the sleeping environment of people who report 'electromagnetic' sensitivity. The primary symptoms included in this as yet unestablished syndrome are insomnia, nausea, vertigo, persistent fatigue, headaches, flu-like feelings, irritability, heart palpitations, respiratory difficulty, diminished concentration, and forgetfulness (Beal, 1998). The durations of these periods of transient electromagnetic fields, often correlated with the usage of power by neighbours or appliances within the house, range between 1 and 10 min and display irregular peaks and troughs with durations of a second to tens of seconds.

There is recent experimental evidence of the sensitivity of nocturnal states, such as sleep, to experimentally applied magnetic fields. Akerstedt et al. (1997) found that all night exposures to 10 mG, 50 Hz magnetic fields reduced the duration of Stage III and IV (slow wave) sleep. More recently Graham and Cook (1999) showed that intermittent but not continuous exposures to 60 Hz fields resulted in less total sleep time, reduced sleep efficiency and attenuated periods of rapid eye movements (dreaming). The subjects exposed to these intermittent fields also reported feeling less well and less rested in the morning compared to the groups that had been exposed to the continuous magnetic fields or to sham fields. Whether or not nightly exposure of humans to these fields would encourage infiltration of immunological cells into the right thalamus, as noted in the present study, remains to be tested.

The importance of the two time constants, $<$ 100 ms and 10 s, within the applied pattern to explain the results observed in our experiments must still be demonstrated by examining the effects of other combinations. If the observations by Litovitz et al. (1997) for cells are correct, then combinations of critical periods or time constants required for cells or clusters of cells to sense the presence of weak complex magnetic fields may differ. The attenuating effect from the 7 Hz square wave field (a time constant of 71 or 143 ms, depending upon use of polarity) upon numbers of foci within the brain but not the 40 Hz field (a time constant of 12.5 or 25 ms, depending upon use of polarity) when both were presented

with the same amplitude modulations demands a greater understanding if these temporal configurations. If the magnetic sensitivity of the rate of the reaction within specific chemical substrates is a mechanism for the detection of weak (nT to μT) magnetic fields as suggested recently by Weaver et al. (2000), then complexity of the temporal pattern of presentation (like the presentation order of pharmacological agonists and antagonists) may be more important than simple intensity once a threshold has been achieved.

Our results also suggest that very weak magnetic fields influence processes associated with cellular immunity, such as autoimmune disorders. Considering the role of ACTH (adrenocorticotrophic hormone) and corticosteroids in the maintenance of the blood-brain-barrier (Paul and Bolton, 1995) and the elicitation of these compounds following inductions of limbic seizures (Persinger et al., 1993), it may be relevant that 7 Hz magnetic field patterns with strengths similar to those employed in the present study increased the numbers of nocturnal seizures in chronic epileptic rats (Persinger, 1996; Michon and Persinger, 1997). Complex, burst-firing magnetic fields with intensities in the order of 5 mG facilitated biting responses, presumably through increasing the release of corticotrophin releasing factor in limbic epileptic rats (St-Pierre et al., 1998).

However, this type of agonistic behavior was attenuated by oral administration of the potential inhibitor of corticotrophin-releasing factor, prednisolone (which binds to Type 1 and Type 2 glucocorticoid receptors) while oral consumption of dexamethasone (which is sequestered primarily by Type 2 glucocorticoid receptors) did not alter the behavior (Bedard and Persinger, 1995). If the CRF, ACTH and corticosteroid system was activated by the 7 Hz, amplitude modulated fields presented in this study, then the attenuation of the numbers of foci throughout the brain may have been promoted by a systemic immunosuppression sensitive to a relatively narrow range of weak intensities.

The numbers of mast cells within the brain also responded to the treatment. Mast cells were not distributed throughout the adult rat brain but were localized primarily within the thalamus of the diencephalon. This observation is similar to other reports (Persinger, 1981; Johnson and Krenger, 1992; Brenner et al., 1994). The results of the present study also indicated there were more mast cells within the brains of rats that had been exposed to the 40 Hz magnetic fields relative to the control condition and 7 Hz, low intensity groups. If we assume the enhanced numbers of these metachromatic, histamine and heparin contain elements within the brain reflect their accumulation during the two weeks of exposure to the 40 Hz fields then our results suggest this frequency induced chemical changes that attracted the concentrations of these mobile intracerbral cells (Persinger, 1977) or encouraged their proliferation within the parenchyma.

Graded or explosive degranulation of mast cells significantly affects the integrity of the blood brain barrier (Persinger, 1977; Orr, 1988; Dietsch and Hinrichs, 1989). An approximately 50% increase in the numbers of mast cells within critical regions of the brain due to transient, nocturnal exposures to magnetic fields might be a 'critical mass' that could initiate a disease process if these cells began to degranulate (Bo et al., 1991) and altered the blood-brain-barrier during periods of generalized immune reactivity induced by environmental toxins or allergens. Because the locations of mast cells in the human brain differ from their location within the rodent brain, one would expect species differences with respect to syndromes and types of diseases that would be displayed.

For example normal human brains, unlike rodents, contain copious numbers of mast cells within the circumventricular organs such as the pineal organ and area postrema as well as the choroid plexuses (Dropp, 1979). These organs are noted for their fenestrated capillaries and less proficient blood-brain-barrier. Histamine and heparin release from mast cells within the area postrema might affect the incidence of malaise with nausea and vertigo. If infiltrations of immunologically reactive cells were encouraged within the surrounding regions, such as the solitary and parasolitary nuclei, then subtle changes in cardiovascular, gustatory and other primarily parasympathetic functions might emerge.

Changes in the densities of mast cells within the pineal organ might influence the metabolism of serotonin or melatonin within this neuroendocrine modulator and affect the dynamics of its intricate vasculature. Melatonin, whose levels within the brain peak during sleep between about midnight and 5 h and whose concentrations can be suppressed by pulsed magnetic fields (Reiter, 1993) is considered a mild endogenous antiepileptic as well as an oncostatic compound (Wilson and Anderson, 1990). Altered levels of melatonin during the winter months have been strongly associated with subtypes of clinical depression (Wilson and Anderson, 1990). If the magnetic fields employed in the present study mediated their effects even partially in a manner similar to stronger fields (Galvanovskis et al., 1999) by influencing the kinetics of calcium oscillations within the cell (Tang and Othmer, 1995), then the high concentrations of calcium salts within the pineal organ of the human (often sufficient to be a reference during examination of CT scans) may also enhance this structure's sensitivity (Jacobson, 1994).

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